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EXECUTIVE SUMMARY

TECHNICAL REPORT

Non-Cancer Effects of PCBs – A Comprehensive Literature Review

April 10, 2001

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[1] Letters from Drs. Bernier, Borak and Palumbo commenting on their review of the Report are set forth in Attachment A.

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I. EXECUTIVE SUMMARY

A. BACKGROUND

The United States Environmental Protection Agency ("EPA") is conducting a reassessment of the non-cancer human health effects of polychlorinated biphenyls ("PCBs").[2] The Report provides -- for the first time in a single document – assessments of the important human non-cancer studies using the EPA-endorsed weight-of-evidence approach. In this Report, the human non-cancer studies are assessed in the context of well-accepted criteria for causation to determine if exposure to PCBs is causally related to any adverse non-cancer effect. EPA should consider thoroughly and carefully the information presented in this Report in its reassessment.

This Report provides a critical review of the 24 studies of the six major cohorts of children that serve as the primary source of data for determining whether PCBs affect growth or neurodevelopment in children. In addition, this Report reviews 84 occupational and environmental studies for causal associations between PCB exposure and effects on 14 different organs or organ systems. The results of these critical reviews are set forth in this Report.

EPA guidance describes how a variety of data, including laboratory bioassays, mode of action data, and human epidemiological studies should be integrated into an evaluation methodology that provides the most biologically relevant end result. Notwithstanding this guidance, to date EPA has derived reference doses (“RfDs”) for use in human health risk assessment based solely on laboratory animal bioassays. This Report provides the most comprehensive compendium of human epidemiological data assessing non-cancer endpoints and should be used by EPA, in combination with laboratory animal studies, to more accurately assess PCB non-cancer toxicity.

The remainder of this Executive Summary describes the results of the Report’s assessment of the studies of the non-cancer health effects of PCBs. For the reader’s convenience, a brief summary of the Report’s results is presented first. A more comprehensive summary follows.

B. BRIEF SUMMARY OF RESULTS

In evaluating human studies, it is important to note that finding an association between exposure to a chemical and an effect does not necessarily imply that the relationship is causal. As EPA and others have recognized, establishing that an association is causal requires satisfaction of a universally recognized set of criteria commonly referred to as “causation criteria.” In the 1996 *Proposed Guidelines for Carcinogenic Risk Assessment*; EPA identifies several factors to be assessed in determining whether an association between exposure to a chemical and a health effect is likely to reflect a causal relationship. These factors include: the appropriate temporal relationship between expo-

[2] 65 Fed. Reg. 1863 (Jan. 12, 2000).

sure and effect; consistent results in independent studies; strong association; reliable exposure data; the presence of dose-related responses; freedom from biases and confounding factors; and high level of statistical significance. This Report applies these and other factors to assess whether there is a causal relationship between PCB exposure and non-cancer human health effects.

1. Neurodevelopmental Effects

Since the middle 1980s, EPA and other groups and individuals have claimed that a growing body of scientific studies suggests that PCBs may cause neurodevelopmental effects in children. In the 1980s, such claims rested on only a few studies that some cited as "suggestive" of an association between child exposure to PCBs and neurodevelopmental effects. Today, there is a much larger body of information that can be used to assess not only whether there is substantial evidence supporting an association, but also whether there is any scientifically credible evidence to support a causal relationship between exposure to PCBs and adverse neurodevelopmental effects in infants and children.

Twenty-four studies of six separate groups of children ("cohorts") now serve as the primary source of data for determining whether PCBs affect early growth or neurodevelopment in children. The general characteristics of the cohorts are presented in the following table. The children's developmental status was evaluated at multiple time points ranging from birth to 11 years of age.

General Characteristics of the Six Cohorts

Cohort Name	Birth Years	No. Papers	No. Children		Presumed Exposure Pathway
			Initial	Last Study	
Michigan	1980-81	8	313	178	Background + Fish[3] + Farm Products
North Carolina	1978-82	5	930	636	Background
Dutch	1990-92	7	418	395	Background
Oswego NY	1991-94	2	559	292	Background + Fish
German	1992-97	1	171	119	Background
Faeroe Is.	1994-95	1	182	182	Background + Fish
Total		24	2,573	1,802	

Fish = contaminated fish consumption.
Background = exposure from undefined sources other than contaminated fish.

The most recent study, of the Faeroe Islands cohort, found no associations between PCB exposure and neurodevelopment, but did find such associations for methylmercury exposure. Although many of the studies of the other cohorts did report associations between exposure to PCBs and certain effects that may be related to neurodevelopment, a careful analysis of the available evidence demonstrates that these reported associations are weak and that there is little evidence for a causal relationship between PCB exposure and the reported effects.

In most of the studies, the exposures to PCBs have been poorly measured, resulting in highly suspect associations. A substantial portion of the associations that were discovered could have been attributed to chance, or explained by any number of confounding factors that were not properly considered in the studies. These confounding factors included both exposures to other chemicals, as well as lifestyle, family and genetic factors, that could cause neurodevelopmental effects. Moreover, there is no strong consistency of outcomes reported within studies, within cohorts and across cohorts, and no dose-response relationships have been convincingly demonstrated. The associations reported are mostly transient in nature, and many of the outcome measurements used in these studies were never intended to detect subtle effects of neurotoxins at low exposures and have not been validated for that use.

A few examples of flaws in the studies assist in understanding why the studies, as a whole, provide little support for a causal relationship between PCB exposure and neurodevelopmental effects:

- Maternal PCB exposure in the Michigan studies was based in part on hospital-bed interviews taken the morning after delivery, when mothers were asked to recall how much fish of particular species from Lake Michigan they had consumed over the previous 14 years. Such recall did not correlate with the PCB levels actually measured in umbilical cord serum. Where PCB umbilical cord blood data was below the PCB quantitation limit -- a problem for nearly 70% of the Michigan cohort -- or where PCB data were missing for individuals, the Michigan authors assigned these individuals PCB exposure estimates using a methodology that was not adequately explained or validated.

- In the Dutch studies alone, over 1,700 comparisons were made in an effort to identify correlations between PCB/PCDD/PCDF exposure and adverse neurodevelopmental effects. On a statistical basis, all "correlations" found could be attributed purely to chance. Further, taken as a whole, over 2,200 comparisons for PCB exposure alone were made by the authors of the Dutch, Michigan, North Carolina, Oswego, German, and Faeroe Island cohorts, but again all correlations could be attributable to chance. The study authors appeared to have highlighted selected adverse correlations and ignored the fact that most of their comparisons did not result in associations between PCB exposure and adverse neurodevelopmental effects.

- Of the outcomes reported to be correlated with a PCB exposure metric, none represents a specific effect that could be readily associated with either specific stages or functions of neurodevelopment, and none of the studies established that the neurodevelopmental outcomes observed were distinguishable from those expected in children typical of the reference population.

- There was substantial inconsistency in the associations reported either within or among cohort studies. For example, in one Michigan study there were both three positive correlations and two negative correlations between PCB exposure and developmental performance, depending on which PCB metric was used. In the North Carolina studies, correlations were found at 6, 12 and 24 months, but not at 18 months or at 3, 4, or 5 years of age, and only in formula fed children (who were presumably exposed to less PCBs than breast fed children). Negative correlations using the Prechtl NOS developmental test were reported for the Dutch cohort, but not for the Faeroe Islands cohort; negative correlations using the Fagan test were reported for the Michigan cohort, while positive correlations were reported for the Dutch cohort; negative and positive findings using the McCarthy tests were reported for the Michigan cohort but no such correlations were found for the North Carolina cohort. None of the studies ever reported that there was any consistency over time among any one child's performance scores on the various neurological tests.

Thus, as discussed in detail in the Report, there is little evidence for a causal association between PCB exposure and neurodevelopmental effects.

2. Other Non-Cancer Effects

Animal bioassays have shown that at elevated doses PCBs are capable of causing a variety of adverse effects. However, many summaries of the toxicology of PCBs fail to critically evaluate the human clinical and epidemiologic literature on PCBs, which rarely shows adverse effects from PCB exposure. The Report provides this evaluation.

The largest cohorts of people who experienced high levels of PCB exposure consist of employees of companies that manufactured electrical capacitors. The duration and magnitude of exposure for these populations were such that most scientists have concluded that studies of these populations provide the best opportunity to detect health effects, if any, that are attributable to PCBs.

Four large manufacturing plants located in the Midwestern and Northeastern U.S. have been studied in detail. These plants employed thousands of people during periods of moderate to heavy PCB use, and several studies have been published that contain extensive clinical data derived from cross-sectional surveys of workers from these plants. To a lesser extent, the health of employees from capacitor-manufacturing plants in other countries has also been studied, but these studies tend to be of lesser significance, either because of the small number of workers evaluated or because the magnitude of PCB exposure was presumed to be lower than that experienced by U.S. workers. Clinical observations have also been obtained from three cohorts of transformer repair workers, two cohorts of PCB manufacturer workers, and one cohort each from silk thread manufacturer workers, marine paint workers, and employees exposed to heat transfer fluids. In addition, 43 clinical studies of environmentally exposed cohorts were reviewed.

Based on the critical review of 84 occupational and environmental studies that sought to determine whether there are causal associations between PCB exposure and effects on 14 different organs and organ systems, the following conclusions were reached:

- Some evidence indicates that ocular and dermal effects, including chloracne, may be causally associated with high levels of occupational exposure to PCBs. It is clear that there is no causal association between chloracne or other ocular and dermal effects and low-level environmental PCB exposure.

- The available human data provide no support for a causal association between PCB exposure and any type of disease or dysfunction of: the liver; serum lipid levels; the cardiovascular or cerebrovascular systems; the immune system; the gastrointestinal tract; the musculoskeletal system; the nervous system; or the reproductive system. In addition, no causal associations were found for PCBs and genotoxicity or an increase in mortality.

C. EXTENDED SUMMARY OF RESULTS

This Report provides an assessment of the non-cancer effects of PCBs. The discussion of the non-cancer effects of PCBs is divided into in two sections: the first assesses neurodevelopmental effects; the second discusses effects on all other human organs/systems that have been studied. In this extended summary of results, we summarize how this Report is structured and the method of analysis used, and we provide a full discussion of the Report's conclusions.

1. Structure and Method of Analysis

The Report presents a formal weight-of-evidence evaluation using "causation analysis" to address whether exposure to PCBs is causally related to an increased risk of non-cancer disease. Causation analysis is most appropriately applied to a group of studies that have investigated potential associations between exposure to a particular chemical and specific disease endpoints. The methodology is well recognized by EPA (1996). The criteria for determining causation, often referred to as "causation criteria" or the "Hill Criteria" (after Hill (1965)), have been developing since Jakob Henle and Robert Koch first introduced the concept in the 19th century (Evans, 1976). The following causation criteria are most commonly used in assessing the association between exposure and disease:

Strength of Association -- Only statistically significant associations between exposure and outcomes are judged to be relevant in a causation analysis. The strength of a reported association can be judged using numerous factors that could potentially strengthen or weaken an inference of association between a putative cause and an effect. These factors include: adequacy of cohort definition, exposure assessment, control of confounding factors and covariables, and statistical analysis; reliability and validity of outcome tests and validity of test administration; and magnitude of measured effect ("effect size").

Dose-Response Relationship -- The conclusion that exposure to a chemical causes an observed effect is undermined if a dose-response relationship does not exist, *i.e.*, if the frequency or severity of the observed effect does not increase with the dose of the chemical. The existence of dose-response, or biological gradient, helps to establish a

causal relationship but it is neither required nor sufficient for proof of such a relationship. A dose-response relationship has its own series of prerequisites, including that there must show a consistent trend in which an increase, or decrease, in exposure is accompanied by a consistent change in effect. Although two points may be considered suggestive of a dose-response relationship, they are insufficient to establish a trend.

Specificity of Association -- The likelihood of a causal inference is increased if an exposure (the putative cause) produces a specific effect (*e.g.*, a specific tumor type or an

unusual disease). Otherwise stated, causation is strengthened where a unique change can be easily related to a single agent, biologic mechanism, or, in this case, an identifiable developmental process, and is not strengthened where the outcome reflects general changes or vague features that are difficult to assign to a particular event or causative agent.

Consistency of Association -- Consistency of association is important because no single epidemiological study is definitive. Associations are consistent when they are seen in several independent studies of similar exposures in different populations, or when they occur consistently for different subgroups in the same study.

Biological Plausibility -- Biological plausibility, or "coherence with existing information," is a determination of whether a particular finding or result makes sense based on knowledge of the disease, the chemical under study, and/or the mechanism of action of the chemical.

Temporality of Association -- For a causative association to be temporally correct, an effect must follow exposure and do so after a biologically appropriate interval. Causation does not exist if the disease predates the exposure.

Whether individual causation criteria are satisfied is often determined by comparison of experimental data to factors that bear on the causation criterion in question. None of the causation criteria, with the exception of temporality, should be considered necessary to establish causation. Each of the causation criteria, however, is important and causation or lack of causation is established by the weight-of-evidence and the extent to which all six criteria are satisfied by the available data.

Given the nature of the studies investigating different non-cancer endpoints, somewhat different approaches to causation analysis are taken in the discussion of neurodevelopmental effects (Section IV.A), and that of all other non-cancer effects (Section IV.B). The discussion of the 24 neurodevelopmental studies of six different cohorts are organized by cohort. Within the cohort discussions, general features that could bear on the quality of the evidence generated by the individual studies are considered first. Then, the studies of each cohort are individually presented. For each cohort, a Cohort Chart shows all of the comparisons that the authors made between measures of PCB exposure and outcomes as well as which comparisons resulted in statistically significant associations. The Cohort Charts are set forth in Attachment C. Each study is evaluated to determine if the causation criteria have been satisfied. After all studies of a cohort have been analyzed, the causation criteria are applied to the studies of that cohort as a whole. Finally, after evaluation of each of the cohorts, the evidence presented by all of the studies of all of the cohorts is considered in a weight-of-evidence evaluation.

Causation analysis is performed in a different manner for studies of other effects. Detailed evaluations of over 80 clinical and epidemiological studies of 14 different non-cancer endpoints are set forth in Attachment B. First, each study is placed into one of

five categories reflecting a judgment as to the relative strength of evidence that the study provides based on cumulative PCB exposure/dose and cohort size. The largest studies of subjects who had demonstrably high PCB exposures are placed in Category A. Category B includes studies containing smaller cohorts of subjects who had exposures that were the same or very similar to those in Category A. Category C consists of studies whose populations had average exposures roughly two to ten times higher than background, regardless of cohort size. Category D includes study populations with relatively low cumulative PCB exposure, again regardless of cohort size. Studies deemed "not classifiable" were placed in Category E.

The studies are then evaluated by non-cancer endpoint. The endpoint evaluated are effects on: the skin and eye; the liver; lipid metabolism; cardiovascular and cerebrovascular function; the respiratory system; hematopoiesis and blood cells; the immune system; the kidneys; gastrointestinal function (other than effects on the liver); the musculoskeletal system; the nervous system; the reproductive system; genotoxicity; and mortality. Within each section addressing an endpoint, the studies are discussed by category. Next, the causation criteria are applied to all of the studies addressing a given endpoint. The categorization scheme allows appropriate weight to be given the more powerful studies. Finally, Section IV.B. of this Report provides a summary of the weight-of-evidence causation analyses for all endpoints.

2. Discussion of Report's Conclusions

a) Neurodevelopmental Effects

Since the middle 1980s, EPA and others have claimed that a growing body of scientific studies suggests that PCBs may cause adverse neurodevelopmental effects in children. Today, there are 24 studies of six cohorts that can be used to assess whether there is substantial evidence supporting such an association, as well as to determine whether there is sufficient scientifically credible evidence to conclude that there is a causal relationship between exposure to PCBs and adverse neurodevelopmental effects in children. The six cohorts are referred to herein as the Michigan, North Carolina, Dutch, Oswego, German and Faeroe Islands cohorts. As discussed below, although several of the 24 studies report associations between PCB exposure and various neurodevelopmental outcome measures, causation analysis leads to the judgment that there is insufficient evidence to support a causal relationship between exposure to PCBs and neurodevelopmental impairment in children.

Four causation criteria – strength of association, specificity of association, dose-response, and consistency of association – are dealt with in our discussions of the cohorts. As noted previously, strength of association can be judged using numerous factors that could potentially strengthen or weaken an inference of association between a putative cause and an effect. In our assessment of strength of association, we address: reliability and validity of outcome measurements and tests; validity of test administration; magnitude of measured effect ("effect size"); and adequacy of cohort defi-

nition, exposure assessment, statistical analysis, and control of covariates and confounding factors. In assessing control of covariates and confounding factors, we looked for control of five covariables important in neurodevelopmental studies (socioeconomic status, parental IQ, use of alcohol and illicit drugs, and smoking) and exposure to three confounding neurotoxicants (lead, methylmercury, and polychlorinated dibenzo-dioxins/polychlorinated dibenzofurans ("PCDD/PCDF").

The analysis of the last two causation criteria, biologic plausibility and temporality of association, is essentially the same for all 24 studies. Consequently, we deal with those criteria first and then provide a cohort-by-cohort analysis of the other factors.

Biologic Plausibility – Based on neurological effects seen in laboratory animals that were highly exposed to PCBs, neurodevelopmental effects in humans may be biologically plausible. It must be noted, however, that the effects reportedly seen in humans are not the same as the effects seen in animals and that the environmental doses received by humans are below those provided to laboratory animals. Nevertheless, the biological plausibility criterion is satisfied.

Temporality of Association – Although it is likely that exposure to PCBs occurred before effects were seen, exposure to many other chemicals can also be inferred to have occurred before effects were seen. Further, none of the studies demonstrated that the PCB metrics that were later reported to be negatively correlated with various neurodevelopmental outcomes were the same as those necessarily required to be present at the time of *in utero* development to initiate a developmental insult. The studies were not able to establish a temporal relationship between exposures and outcomes because no samples were taken during early to mid pregnancy and, even if they had been, the period during which the developing fetus is susceptible for the purported effects is not precisely known. Since temporality of association is a strict requirement of a causation inference, this criterion is deemed not satisfied.

(1) The Michigan Cohort

Three hundred thirteen children and their mothers who lived near Lake Michigan during pregnancy were studied. The authors have published eight papers studying the neurodevelopment of the "Michigan Cohort." The studies sought to determine whether consumption of contaminated Lake Michigan fish resulted in maternal PCB levels sufficient to impair the normal development of their children. In the course of the study at least nine different measures, or metrics, of PCB exposure were used. The authors sought correlations between one or more of these metrics and at least 39 outcome measures including measures of growth and scores on behavioral, psychological and intelligence tests. The comparisons made by the authors, as well as the results of those comparisons, are shown on Chart 1 -- Michigan Cohort (Attachment C).[4] Of the numerous comparisons made by the authors, relatively few associations between PCB exposure metrics and outcome measures were found.

The findings of the Michigan studies do not support an associative or causal relationship between PCB exposure and the selected growth and neurodevelopmental effects. The strength of association shown by these studies is very weak. First, selection bias resulted in a non-random cohort, misclassification bias was present due to poor characterization of the PCB exposures of cohort subgroups used for comparisons, and the composition of the cohort changed substantially over the course of the studies. Second, the PCB exposure of the cohort was very poorly characterized. All of the PCB exposure metrics used in the Michigan studies were so inaccurate that one can have no confidence that the various comparisons made in the studies were actually among children with different levels of PCB exposure. Third, most of the studies did not properly distinguish between PCB exposure and exposure to important covariates and confounding factors, including lead, methylmercury, and PCDD/PCDF. The one study that did measure lead concentrations in the children's blood found that lead concentrations correlated well with the neurological deficits that were reported. Fourth, the studies did not take steps to minimize the possibility of Type 1 error (*i.e.*, finding a statistically significant association when, in fact, it is not present). Fifth, several of the neurobehav

[4] Associations between a PCB exposure metric and an outcome measure that the authors reported to be statistically significant are shown by pink boxes on the Cohort Charts. Yellow boxes indicate that no statistically significant association was found. White areas indicate that it is unknown whether comparisons were made between exposure metrics and outcome measures. Additional explanations of how to use the Cohort Charts are found at the beginning of Attachment C and on the charts themselves.

ioral tests employed in the studies lacked the validity, reliability and sensitivity to detect the minor effects reported in the studies, and test administration was only sometimes validated. Finally, the effect size reported in the studies was small. Thus, the strength of association is very weak for this series of studies.

The dose-response criterion is not satisfied because, although some of the studies claim that an occasional dose-response relationship was found, careful analysis refutes this claim. Most importantly, no claim of dose-response can be supported given that both the maternal recall of fish consumption and the PCB cord blood metrics poorly quantified PCB exposure. Moreover, claims of dose-response were based on comparisons of the mean scores of groups defined by arbitrary PCB exposure "cutoffs," the groups were defined using different cutoffs in different studies, and the high-dose group always contained far fewer individuals than the low-dose group or groups. Generally the claim of dose-response was based on comparing only two dose groups, even though the authors typically defined four such groups. These facts strongly suggest that chance could well be responsible for the apparent dose-response relationship.

The specificity of association criterion is not satisfied because virtually all of the reported associations are between PCB exposure metrics and nonspecific effects – that is, performance on tests of general abilities rather than measurements of specific neurological or neurodevelopmental endpoints.

The Michigan studies also show little consistency of association in the relationship between PCB exposure and neurodevelopmental effects. Since no single exposure metric was consistently used throughout the series of studies, it is difficult to correlate early findings with later findings and assess the series of studies for consistency of association. To the extent it is possible to assess consistency, it is evident that the data do not show any particular PCB exposure metric to be consistently associated with neurodevelopmental outcomes. If PCB exposure were truly associated with (or caused) neurodevelopmental effects, one would at the least expect a PCB exposure metric to be much more consistently associated with the various measures of the same or similar performances or abilities. In fact, since several of the authors' various exposure metrics were intended to estimate the same exposure (prenatal or postnatal PCB exposure), the exposure measures (either prenatal of postnatal) should correlate both among themselves and with outcome measures. This type of correlation is almost totally lacking in the Michigan Cohort studies.

Importantly, the authors never report that there was any consistency over time among individual children's performance scores on the various neurodevelopmental tests. If it were shown that children with higher PCB exposure consistently scored lower on neurodevelopment tests, one might be persuaded that PCB exposure was associated with the lower test scores. However, the authors never present any findings in this regard. It therefore seems fair to assume that individual children who may have had higher PCB exposures did not consistently perform poorly on tests. If this assumption is correct, the reported findings are more likely explained by some factor(s) other than PCB exposure.

Finally, all of the differences between the performance of the "exposed" and "unexposed" groups are minor and all of the children in the cohort performed within the ranges expected in the general population. In fact, the children performed above the standard population median in most cases. Thus, even if the authors' findings are accurate, the inconsistency of the findings and the small effect size tend not to support a causal relation between PCB exposure and neurodevelopmental effects.

(2) The North Carolina Cohort

The North Carolina Cohort study enrolled 931 children born to 880 women between 1978 and 1982. The authors have published four papers on the cohort that assess neurodevelopment and one that assessed growth. In the papers, at least three different metrics of PCB exposure were used and the authors sought correlations between one or more of these metrics and at least 21 outcome measures at different points in time. The results of the comparisons are shown on Chart 2 -- North Carolina Cohort (Attachment C).

The North Carolina studies provide insufficient evidence to support a causal relationship between PCB exposure and neurodevelopmental effects. The reported strength of association is weak. The cohort did not well represent the target population. Selection bias was introduced because, as the authors admitted, they used a non-random participant selection process. PCB concentrations in maternal serum and milk – which were used to derive the authors' exposure metrics -- were not determined fully and were not measured with precision and accuracy. The analytical procedure used by the authors measured only about 25% of the total PCBs likely to be present in blood and milk samples. Moreover, lack of correlations among measures of PCB exposure strongly suggest that significant analytical error was present. In addition, the only reported associations in these studies were with the prenatal "PCB milk fat index." This exposure metric was derived using a procedure that is not coherently described by the authors and, at best, is an indirect estimate of PCB exposure. Thus, it is apparent that the relative PCB exposures of cohort participants were not adequately determined. The studies also did not properly account for important covariates and confounding factors (including exposure to lead, methylmercury, and PCDD/PCDF) and did not take steps to minimize the possibility of Type 1 errors. Only some of the neurodevelopmental tests administered were tested for reliability and validity and those were determined to have modest reliability and predictive capacity. Finally, the effect size reported in the studies was small (*i.e.*, differences between the performance of the "exposed" and "unexposed" groups are minor and all of the children in the cohort performed within the ranges expected for the general population). Thus, the strength of association criteria is weak for this series of studies.

The studies also fail to fully satisfy the remaining causation criteria. There is only a slight suggestion of dose-response in some studies, and then only when the highest exposure groups, containing very small numbers of individuals, are compared with the

lowest dose groups. Careful analysis refutes any credible claim of dose-response. The specificity of association criterion is not satisfied because most of associations reported were between PCB exposure metrics and nonspecific effects.

Finally, the studies show little consistency of association. Correlations between outcome measures and higher PCB exposure were found only occasionally with only one of the authors' two prenatal PCB exposure metrics. No correlations were found between postnatal exposure metrics and outcome measures. The associations that were reported were transient and had limited apparent influence on later performance. As in the case of the Michigan studies, the authors never report that there was any consistency over time among any one child's performance scores on the neurodevelopmental tests. Furthermore, comparing the exposure metrics and outcome measures used in the studies of the Michigan and North Carolina studies, as well as the results of the two series of studies, it is apparent that the North Carolina studies can not be interpreted as reproducing the results of the Michigan studies.

(3) The Dutch Cohort

The cohort in this series of studies included 418 mother-child pairs who were enrolled from June 1990 to February 1992. 207 pairs were from Rotterdam and 211 were from the city of Groningen. The authors have published eight papers on the cohort. As shown in Chart 3 -- Dutch Cohort Chart and Chart 4 – Dutch Cohort: Growth Measures of Children (Attachment C), at least 70 different metrics of PCB exposure were used in the course of the studies and the authors sought correlations between one or more of these metrics and over 30 outcome measures. Both charts make clear that the associations reported by the Dutch studies were sporadic, limited, and highly inconsistent

The Dutch studies do not support an associative or causal relationship between PCB exposure and neurodevelopmental effects. First, the strength of association must be judged as weak. There was bias in cohort definition derived from at least five sources of either selection or misclassification bias. The studies' exposure assessment was adequate in quantifying the parameters that were measured, but the data are of limited use in assessing environmental PCB exposure. The cord blood and maternal serum prenatal PCB exposure metrics were based on quantification of only four PCB congeners. Although numerous PCB congeners, dioxins and furans were measured in maternal milk and these measurements were used to derive numerous exposures metrics, none of these metrics represents total PCB exposure. Moreover, the use of numerous metrics to make multiple comparisons substantially increased the probability of associations appearing due to chance alone. In fact, in most cases appropriate adjustment for multiple comparisons would have revealed that the reported associations were not statistically significant. The authors also failed consistently to control for important covariates (socioeconomic status, parental IQ, alcohol use, illicit drug use and smoking) and chemical confounders (exposure to lead, methylmercury, and PCDD/PCDF). Only some of the neurobehavioral tests employed were tested for reliability and validity, all of the tests lacked the sensitivity necessary to detect the effects that were reported in the

studies, and in no study was test administration validated. Finally, the effect size reported in the studies was small. Thus, the strength of association criteria is weak for the Dutch studies.

Four of the seven Dutch studies appear to provide some suggestion of dose-response, but further analysis casts serious doubt on whether any dose-response is present. The Dutch studies also fail to fully satisfy the specificity of association criterion. Most of associations reported were between PCB exposure metrics and nonspecific effects.

Finally, the consistency of association criterion is clearly not satisfied. Relatively few negative associations between exposure metrics and outcome measures were found and the results of the studies are strikingly inconsistent.[5] For example, sometimes outcomes reportedly correlated only with prenatal exposure and sometimes they correlated only with postnatal exposure. As another example, sometimes outcomes correlated with prenatal PCB exposure represented by the studies' cord blood metric but not the studies' maternal serum metric or various breast milk metrics. If PCB exposure was truly associated with (or caused) neurodevelopmental effects, one would expect the same metric to be consistently associated with similar performance measures. Moreover, as in the case of the Michigan and North Carolina cohorts, the studies do not report that there was any consistency between individual children's exposure and their results on the various neurological tests that were administered over the period of the study. It is also important to note that all of the differences between the performance of the "exposed" and "unexposed" groups are minor, that all of the children in the cohort performed within the ranges expected for the general population, and that the studies show that the most important factors associated with the neurodevelopment of children are related to maternal factors other than chemical exposure. Thus, the low strength of association, the inconsistency of the findings, and the small reported effect size tend not to support a causal relation between PCB exposure and neurodevelopmental effects.

(4) The Oswego Cohort

The Oswego cohort included 559 infants whose mothers reported consuming different amounts of Lake Ontario fish. Two studies of the cohort have been published to date. The comparisons made by the authors and their results are shown on Chart 5 -- Oswego Cohort (Attachment C).

The Oswego studies do not support a causal relation between PCB exposure and neurodevelopmental effects. The first study used differences in scores over time on seven "clusters" of the Brazelton Neonatal Behavioral Assessment Scales ("NBAS") as their outcome measures. Although the authors suggest that they found an association between PCB exposure and changes in scores over time, little evidence supports this

[5] Note the prevalence of white areas on the Dutch Cohort Chart. It seems likely that the authors made many more comparisons than they report. Presumably, no associations were found for these additional comparisons.

claim and virtually no evidence points to a causative role for PCBs. The strength of association must be judged as very weak. The only exposure metric used in the first study was based on maternal recall of fish consumption. No analytical results for PCBs or other chemicals were provided or used in comparisons. There is no evidence that children placed into different exposure groups based on maternal recall of fish consumption actually differed in PCB exposure or that the effects reported in the study were due to PCB exposure. The second study evaluated the NBAS scores taken at two time points separately and quantified PCBs and other chemicals in cord blood; however, cord blood samples were available for less than one-third of the cohort. The second study's exposure assessment was adequate in quantifying the parameters that were measured, but the findings are very limited -- two of seven NBAS cluster scores were reportedly associated with one of the four exposure metrics. The limited findings of this study cannot be given much weight due to the small size of the cohort (n=119). Only 40 children in this cohort had PCB exposure that was high enough to place them in the "high" exposure group for which an association between NBAS scores and PCB exposure was claimed. In neither study did the authors control for all five important covariates and all three confounding factors (including exposure to lead, methylmercury and PCDD/PCDF).

The authors point out a limitation of their studies that bears on the strength of association: the NBAS was designed to evaluate the development of children in high-risk groups (*i.e*., following obstetric medication or substance abuse) and its predictivity when used for non-risk population is limited. Although the authors indicate that the NBAS is *"limited in its predictive validity,"* they suggest that repeated administrations of the NBAS has better predictive validity. However, in their studies, the authors administered the NBAS three times over a period of 48 hours and used the *differences* in scores between 24-hour periods as their outcome measures. The authors provide no support for the implicit proposition that changes in NBAS scores over a 24-hour period have any predictive validity. The NBAS was not designed to measure changes that could be expected to be seen from one day to the next (Slikker, Jr. and Chang, 1998). Moreover, although the authors reported limited associations between PCB exposure and *changes* in NBAS scores, it is important to note that no significant differences were demonstrated between exposure groups on the actual scores on any of the seven NBAS clusters at either of the two time points.

Strength of association is further weakened by failure to correct for multiple comparisons (such corrections were made in the first study but not the second), small effect size, and selection bias in cohort definition. The authors of the Oswego studies demonstrate statistically that their cohort was not representative of their target population.

The Oswego studies also fail to fully satisfy additional causation criteria. There is no specificity of association since the associations reported were between PCB exposure metrics and nonspecific effects. Neither of the Oswego studies contains evidence of dose-response. Finally, although the results of the two studies cannot be said to be in-

consistent, the consistency of association criteria is not satisfied because the exposure metrics used in the studies are different.

(5) The German Cohort

The German cohort consisted of 171 mother-infant pairs who were recruited from three hospitals in Dusseldorf, Germany. One study of the cohort has been published. The authors used four PCB exposure metrics. The outcome measures used were scores on two scales of the Bayley Scales of Infant Development (the "MDI" and the "PDI") and on the Fagan Test of Infant Intelligence. The comparisons made by the authors and their results are shown on Chart 6 -- German Cohort (Attachment C).

The authors' findings do not support a causal relation between PCB exposure and neurodevelopmental effects. Although the authors suggest an association between PCB exposure and limited neurodevelopmental effects, the strength of association is weak. The findings of the study were very limited. The authors indicate that the cohort was selected using nonrandom procedures. The only association was between one of the four PCB exposure metrics (the average of the concentrations of three PCB congeners in breast milk at two and four weeks after birth) and one of three outcome measures (the Bayley PDI). This association seems questionable because neither the PDI nor any other outcome measure was associated with the concentrations of the three PCB congeners in breast milk at either two or four weeks after birth. Although the studies' exposure assessment was adequate in quantifying the parameters that were measured, the data are of limited use in assessing environmental PCB exposure. The exposure metrics used in the study were based on quantifying only three PCB congeners. Together these congeners would be expected to represent less than half of the total PCBs in either blood or milk. Thus, any conclusions that relate an effect to total PCB exposures are weak at best. The authors also made multiple comparisons without correction for statistical power. With correction, there are no statistically significant correlations. Further, the authors did not control for all important covariates and confounders. Finally, the effect size reported in the study was small. Thus, the strength of association criteria is weak for the German study.

The German study also failed to satisfy other causation criteria fully. Dose-response was not demonstrated by the study. The specificity of association was weak because the only association reported was with nonspecific effects. Finally, the consistency of association criteria is not satisfied. The findings of this study are inconsistent with those of the Michigan, North Carolina, and the Dutch cohorts that did not find associations between postnatal PCB exposure and the PDI, but rather reported associations between prenatal PCB exposure and the MDI.

(6) The Faeroe Islands Cohort

The participants in this study were 182 children born consecutively during a 12-month period from 1994 to 1995 in a hospital in the Faeroe Islands. One study has been published on the Faeroe Islands cohort. The authors used two PCB exposure metrics,

three methylmercury exposure metrics, and two DDE exposure metrics. The only outcome measure was infant neurological optimality score (NOS) based on the technique described by Prechtl (1980). The study findings are summarized in Chart 7 – Faeroe Islands Cohort (Attachment C).

The authors reported that mercury concentration in cord blood was significantly and negatively correlated with NOS. None of the PCB or DDE exposure metrics were correlated with NOS. Since the authors found no association between PCBs and NOS, but did find an association between mercury and NOS, they suggest the importance of methylmercury as a chemical confounder in the other cohort studies. The authors further point out that the PCB levels in their samples were about three times higher than those seen in the Dutch studies, further suggesting that PCBs are not causing the effects seen in the other cohort studies.

b) Causation Analysis

The results of the causation analysis applied to neurodevelopmental studies taken as a whole are described below and are summarized in Chart 8 – Causation Analysis (Attachment C).

(1) Strength of Association

As noted above, the following factors were used in evaluating strength of association: adequacy of cohort definition, exposure assessment, control of confounding factors, and statistical analysis; reliability and validity of outcome tests and validity of test administration; and magnitude of measured effect.

Adequacy of cohort definition: All of the cohorts had some degree of selection bias and/or misclassification bias. The Michigan Cohort is particularly biased towards consumers of Lake Michigan sports fish, as this behavior was a prerequisite of study participation. Selection bias in the Michigan Cohort is evident in that no significant PCB exposure differences were observed between fisheaters and non-fisheaters. Selection bias also resulted from the fact that the Michigan Cohort was substantially redefined in each of the studies. Misclassification bias resulted from use of interviews to obtain exposure information and use of exposure indices that may not have been related to actual exposure.

The Dutch, German, and North Carolina cohorts were also not representative of their target populations. This is due to selection bias introduced by the participant selection process. The authors of the North Carolina and German Cohort studies admit that their cohorts were not representative, primarily from the manner by which the study populations were selected.

The Oswego Cohort was not representative of its target population because of both selection and misclassification bias. Selection bias was introduced by the manner of

participant selection and resulted in a cohort particularly biased towards consumers of Lake Ontario sports fish, as this behavior was a prerequisite of study participation. Misclassification bias resulted from the use of interviews regarding fish consumption.

The Faeroe Island Cohort was probably the most representative of the six cohorts due to the relatively large size of the cohort compared to the Faeroe Islands population. Moreover, since exposure was based on analytical values for PCBs rather than recall of fish consumption, misclassification was less likely to occur.

With few exceptions, the statistical analyses used in all the cohorts were regression analyses of PCB exposure estimates against neurodevelopmental outcomes. This reduced the risk of misinterpretation due to unwarranted assumptions which is usually associated with comparing two selected groups such as in case-control cohort designs (Rothman and Greenland, 1998). Furthermore, most studies considered multiple covariables (such as maternal education, socioeconomic status, and several maternal behavior characteristics) that would act to reduce the impact of selection bias. Thus, while significant selection bias was likely present in five of the cohorts (with the exception of the Faeroe Island Cohort), the methods of data analysis used in the studies probably reduced its overall impact. Nevertheless, the level of uncertainty about the amount of bias present in the five cohorts leads to the judgment that only the Faeroe Islands Cohort represents its target population and is without significant selection or misclassification bias. Thus, due to the likely presence of bias in the representation of their target populations, cohort definition does not support the strength of association criterion.

Exposure determination: For strength of association to be high, exposure must be accurately quantified. Since each of the studies quantified PCB exposure differently, and since none of the cohort studies quantified total PCB exposure, one can come to no conclusion regarding whether any neurodevelopmental effect is associated with, or caused by, total PCB exposure. Thus, the only questions that may be answered by the cohort studies are whether exposure to various subsets of PCB congeners, in the unknown presence or absence of other PCB congeners and other chemicals, is associated with neurodevelopmental effects.

This very important problem aside, one of many prerequisites for determining whether there are true associations between exposure to subsets of PCB congeners and neurodevelopmental effects is knowing that the exposure metrics were accurately and precisely measured. The cohort studies had variable success in quantifying their various exposure metrics. All of the exposure metrics used in the Michigan cohort were poorly characterized throughout all of the studies. Exposure assessment in the North Carolina Cohort was similarly weak in that, although some PCB congeners were measured, vaguely described indices and estimates of exposure were used as PCB metrics. The various partial exposure metrics used in the Dutch studies, the German study, the Faeroe Islands study, and the Oswego study that used measurements of PCB homologues as a metric have fewer limitations. The exposure metrics in these studies were adequately determined, but represent only a few PCB congeners making it impossible to

draw any conclusion regarding an associative or causal relationship between "total PCB exposure" and any effect.

Covariables: Although multiple covariables were considered in the studies of each of the six cohorts, none of the 24 studies controlled for all five of what may be the most important covariables in studies of neurodevelopment: socioeconomic status, parental IQ, use of alcohol and illicit drugs, and smoking. This fact weakens any putative associative or causative relationship between PCB exposure and any effect.

Confounder control: Although several confounding factors were considered in the studies of each cohort, none of the studies controlled for all three important confounding neurotoxicants (lead, methylmercury and PCDD/PCDF). Lead was only controlled in one study. Failure to control adequately for chemical confounders is a fatal flaw that cannot be out-weighed by any strengths derived from the remaining causation criteria and prevents any inference of causality.

Reliability and validity of outcome measures: Almost one-half of the studies used outcome measures that had not been validated and tested for reliability. This weakens any putative associative or causal relationship between PCB exposure and any effect.

Validation of test administration: Only four of the Michigan Cohort studies, one of the Oswego Cohort studies and the German Cohort study tested for examiner performance and found it to be adequate. This fact weakens any putative causative relationship between PCB exposure and any effect.

Statistics: Many of the statistical methods used in the studies have weaknesses that were generally not considered by the authors in their data interpretation. Most importantly, the statistical analyses generally suffered from low power due to the combination of samples in the formation of exposure groups and the generation of Type 1 errors from the failure to correct for repeated use of data from the same sample in multiple comparisons. These statistical problems weaken the putative association between PCB exposure and effects.

Effect size: None of the cohort studies reported a large effect size. None of the cohorts established that the neurodevelopmental outcomes observed were distinguishable from those expected in a sample of children typical of their reference population. Thus, the effect size seen in these studies does not help in establishing a causal association between exposure and effect.

(2) Dose-Response

Some of the studies reported no dose-response. Others reported dose-response relationships, but did not establish that they were statistically significant and/or failed to demonstrate that there was a decreasing trend in scores with increasing exposure. Still others purported to show statistically significant dose-response relationships, but found

such relationships only between a low dose group and a high dose group that was arbitrarily established and contained only a small number of individuals. Finally, given the studies' problems with exposure assessment (particularly in the case of the Michigan and North Carolina cohorts) and the fact that exposure must be accurately characterized to support a claim of a dose-response relationship, one cannot conclude that any of the studies established a dose-response relationship between PCB exposure and any outcome measure.

(3) Specificity of Association

Of the outcomes reported to be correlated with a PCB exposure metric, none represents specific effects that could be readily associated with either specific stages or functions of neurodevelopment. None of the cohorts established that the neurodevelopmental outcome observed was distinguishable from that expected in children typical of the reference population. Thus, the specificity of association seen in these studies does not help in establishing a causal association between exposure and effect.

(4) Consistency of Association

The best evidence for consistency of association would be findings that the same exposure metric was correlated with the same effect both within a single cohort and across several cohorts. The corollary is that if an exposure metric is found not reproducibly correlated with the same outcome measure either within the same cohort or across cohorts, one must conclude that there is no consistency between exposure and effect, regardless of other evidence. Since the studies of each cohort used different PCB exposure metrics and since there was no attempt to determine how well the metrics correlated among cohorts, it is not possible to establish consistency of findings across cohorts with any certainty. There was also little consistency within studies of the same cohort. The cohort charts for the Michigan, North Carolina and Dutch cohorts reveal a pattern of striking inconsistency. The German, Oswego and Faeroe cohorts do not provide evidence for consistency since correlations with the same metric have not been demonstrated for more than one neurodevelopmental test. Finally, it is important to reiterate that none of the authors ever report that there was any consistency over time among any one child's performance scores on the various neurological tests.

(5) Biologic Plausibility

Based on neurological effects seen in laboratory animals that were highly exposed to PCBs, neurodevelopmental effects in humans may be biologically plausible. Although the effects reportedly seen in humans are not the same as the effects seen in animals and the environmental doses received by humans are below those provided to laboratory animals, it is reasonable to infer that the same or similar effects could occur in humans. Thus, the biological plausibility criterion is satisfied.

(6) Temporality of Association

Temporality of association is clearly a prerequisite to a causal relationship. Since one of the hypotheses of the studies is that PCBs cause effects at the early stages of embryological and fetal development, all of the studies were deficient in failing to measure maternal PCB levels before conception. Although it may be reasonable to infer that PCB exposure prior to conception did occur, it is also reasonable to infer that there was also exposure to many other chemicals, only some of which may be present at the time of blood sampling. Since none of the studies demonstrated that exposure to any particular PCB metric occurred before effects were seen, temporality of association cannot be reasonably inferred from the studies. Thus, the temporality of association criterion is deemed not satisfied.

Causation analysis leads to a final judgment that there is insufficient evidence to support a causal relationship between exposure to PCBs and neurodevelopmental impairment in children. It cannot be concluded that PCBs cause adverse neurodevelopmental effects.

c) Non-Cancer Effects Other than Neurodevelopmental Effects

For the last two decades, PCBs have been widely studied. As in the case of many chemicals, animal toxicology studies have shown that PCBs are capable of causing a variety of adverse effects at elevated doses. However, many summaries of the toxicology of PCBs fail to evaluate critically the clinical and epidemiologic literature on PCBs, which infrequently shows adverse effects from PCB exposure. This Report provides such an evaluation.

Clinical studies of the potential health effects of PCBs have been conducted in three distinct types of study populations. The first type consists of unique populations in Japan (Yusho) and Taiwan (Yu-Cheng) which were exposed through the consumption of cooking oils into which PCB fluids had leaked. These fluids were later found to be heavily contaminated by a much more toxic group of chemicals, polychlorinated dibenzofurans (PCDFs). Subsequent studies in humans and animals have shown that PCBs contributed little, if anything, to the observed health outcomes of these populations.

The second type of study population consists of persons exposed to PCBs found in the environment. Typically, the source of exposure is nearby soils or locally caught fish. While these studies have value in the evaluation of the human health effects of PCBs, they are frequently and severely limited by low or equivocal PCB exposures and/or the presence of other chemicals and risk factors that may confound and limit the interpretation of the studies' results. In particular, those studies using fish consumption as an indirect measure of PCB exposure are generally confounded by the co-presence of other toxic chemicals in the fish, some of which pose well-characterized human health hazards. Thus, caution should be exercised when reviewing these studies. Without elimination of confounding factors and potential study biases, and without confirmation by

other studies, environmental studies must be accorded little weight in the final analysis of a particular toxicological endpoint.

The third type of study population consists of people who were occupationally exposed to PCBs, particularly people exposed before the use of PCBs was severely restricted or discontinued. Numerous studies have examined PCB-exposed workers, some of whom were exposed for decades to levels of PCBs in the workplace that were 10 to 1,000 times higher than the concentrations now found in the general environment. The duration and magnitude of exposure of these populations were such that most scientists have concluded that studies of these populations provide the best opportunity to detect health effects, if any, that are attributable to PCBs.

The largest cohorts of persons who experienced appreciable PCB exposure in the workplace consist of employees of companies that manufactured electrical equipment. Four large capacitor-manufacturing plants located in the Midwestern and Northeastern U.S. have been studied in detail. These capacitor-manufacturing plants employed thousands of people during periods of moderate to heavy PCB use, and several studies have been published that contain extensive clinical data derived from cross-sectional surveys of workers from these plants. To a lesser extent, the health of employees from capacitor manufacturing plants in other countries has also been studied. These studies tend to be of lesser significance, either because of the small number of workers evaluated or because the magnitude of PCB exposure was probably lower than that experienced by U.S. workers. Clinical observations have also been obtained from three cohorts of transformer repair workers, two cohorts of PCB manufacturer workers, one cohort of silk thread manufacturer workers, one cohort of marine paint workers, and one group of employees exposed to heat transfer fluids. These cohorts were, in general, considerably smaller than the U.S. capacitor manufacturing worker cohorts.

This Report reviews and critically evaluates over 80 occupational and environmental studies for causal associations between PCB exposure and effects on the following organs or organ systems: skin and eye, liver, serum lipids or lipoproteins, cardiovascular/cerebrovascular system, lungs, blood, immune system, kidneys, gastrointestinal tract, musculoskeletal system, nervous system, genotoxicity, reproductive system, and mortality. (Section IV.B. and Attachment B). This Report's conclusions are summarized as follows:

Skin and Eye Effects: Although there is evidence that some oculodermal conditions (e.g., eye irritation and burning, dermatitis) and possibly chloracne may be associated with high-level, occupational PCB exposures such as those once seen in capacitor manufacturing plants, one cannot conclude that PCBs caused these conditions for the following reasons: (a) a definitive diagnosis by a dermatologist or ophthalmologist was absent from most, if not all, studies; (b) there are no data to support an objective dose-response relationship between PCB exposure and oculodermal effects, including chloracne; (c) the lack of a dose-response relationship may stem from significant variations in human susceptibility, the potential misclassification of cases, or the failure to account

for potentially confounding doses of PCDFs, chlorobenzenes and/or additives; (d) some skin and eye conditions (e.g., dermatitis, eye irritation and burning) were more likely caused by concomitant exposure to solvents and other chlorinated compounds (e.g., chlorinated benzenes in studies of transformer repair workers). Most importantly, however, it is clear that no oculodermal effects, including chloracne, have ever been reported in environmental studies other than minor, transient skin irritation and redness thought to be due to direct contact with transformer fluid.

Liver Effects: Although liver effects have been the focus of many high-dose animal studies, the clinical and epidemiology studies provide insufficient support for concluding that PCBs cause liver disease in humans, even at relatively high cumulative doses. Specifically, the available studies do not provide sufficient evidence that PCB exposure is causally associated with the induction of liver enzymes, liver injury, or liver disease in humans, even at the high doses experienced by occupational cohorts. No strong, consistent or unequivocal associations were reported in the literature regarding the potential for PCBs to induce liver microsomal metabolism. The only high-dose occupational study reporting evidence suggestive of liver enzyme induction was confounded by abnormally low enzyme activity in its control group. Moreover, given that high occupational exposures no longer exist, it is more important to note that no convincing evidence of induction was observed in studies involving either low-occupational or environmental exposure to PCBs. It should also be noted that liver enzyme induction should be considered an adaptive response rather than an adverse health effect.

There is virtually no evidence that high, occupational PCB exposure causes liver injury or disease. Although a few inconsistent correlations have been reported between serum PCB concentrations and serum transaminase levels, these correlations were seen even when there were no measurable increases in serum liver enzyme activities. These correlations may simply represent mutual relationships among these enzymatic tests, serum PCB levels, and serum lipid levels.

Good health and a lack of significant liver findings have been observed in heavily- exposed occupational cohorts, including those with additional risk factors such as obesity. The thresholds for hepatotoxicity extrapolated from rodent studies are well above those experienced in past occupational settings. Therefore, while high-dose animal studies have suggested that it is biologically plausible that at some dose (higher than that experienced occupationally) PCBs may adversely affect liver function, neither the collective animal nor human studies suggest that this would be a reasonable concern at doses associated with environmental exposure. Thus, after evaluating the studies reporting liver function test measurements and physical/medical examinations in both occupationally- and environmentally-exposed persons, no causal associations can be established between PCB exposure and the induction of liver enzymes, liver injury, or liver disease in humans.

Effects on Serum Lipid Levels: To determine whether the literature supports an association between PCB exposure and effects on serum lipid levels, 20 clinical studies

were examined. Of the 20 studies, 13 involved occupational PCB exposure and seven involved environmental PCB exposure. The lipophilic nature of PCBs inherently leads to the partitioning of PCBs to fatty tissues and lipid-rich organs in the body. This normal partitioning seems to have led a number of studies to report positive correlations between serum PCB levels and serum lipid levels. However, it is now well-recognized that serum lipid levels influence serum PCB levels, rather than that serum PCB levels influence serum lipid levels. Moreover, there is no demonstrable excess of clinical disease where PCB exposure has been reported to alter lipid metabolism or blood lipid levels in either the high-dose occupational cohorts or in populations experiencing lower PCB exposures via the environment.

Cardiovascular Effects: To determine whether the literature supports an association between PCB exposure and cardiovascular effects, 12 clinical studies and 14 mortality studies were examined. Of the 12 clinical studies, six involved occupational PCB exposure and six involved environmental exposure. There is no consistent or strong evidence that either high-dose occupational PCB exposure or low-dose environmental PCB exposure causes any increase in mortality from cardiovascular or cerebrovascular diseases. There is also no consistent or strong evidence that PCB exposure causes an excess of clinical hypertension, electrocardiogram abnormalities, or other physical or functional problems of the cardiovascular system that might ultimately produce an increase in cardiovascular disease mortality.

Effects on the Lungs: To determine whether the literature supports an association between PCB exposure and pulmonary effects, eight clinical studies and nine mortality studies were examined. Of the eight clinical studies, five involved occupational PCB exposure and three involved environmental PCB exposure. No excesses in mortality or morbidity from diseases of the respiratory tract were observed in populations exposed to commercial PCB mixtures. In the clinical surveys of highly-exposed workers, physical examinations, chest X-rays, and pulmonary function tests failed to reveal any excess of clinical abnormalities or dysfunction of the respiratory tract that was not confounded or explained by cigarette smoking, asbestos exposure, or measurement bias. The only study that initially reported an apparent excess of restrictive lung function changes was unable to identify any dose-response relationship, was flawed by measurement error, and has been superceded by subsequent analyses. Studies of environmental PCB exposure that examined respiratory disease rates and/or pulmonary function test results likewise found no excess of clinical abnormalities associated with PCB exposure or PCB body burden measurements.

Effects on the Blood: To determine whether the literature supports an association between PCB exposure and effects on the blood, nine clinical studies and one mortality study were examined. Of the nine clinical studies, seven involved occupational PCB exposure and two involved environmental PCB exposure. No excess mortality or morbidity from diseases of the blood and blood-forming systems was observed among populations highly-exposed to commercial PCB mixtures. The overwhelming majority of clinical studies of persons exposed to PCBs either occupationally or environmentally

found all hematological parameters to be within their expected or normal ranges. No consistent excesses of hematological abnormalities or consistent correlations between blood counts or blood diseases and PCB exposure have been reported.

Effects on the Immune System: Thirteen clinical studies and one mortality study were examined to determine whether there is an association between PCB exposure and effects on the immune system. Of the 13 clinical studies, seven involved occupational PCB exposure and six involved environmental PCB exposure. The available evidence suggests that PCB exposure does not cause immunotoxic effects either in occupationally or environmentally exposed populations. There were no excesses of morbidity or mortality from non-cancer diseases resulting from changes in, or damage to, the immune system among human populations exposed to commercial PCB mixtures. Large clinical studies of both highly-exposed occupational cohorts and lesser-exposed environmental cohorts examined blood counts and performed serum immunoglobulin assays, skin antigen testing for delayed type hypersensitivity, and T cell subset analysis. No excesses of clinical abnormalities or diseases of the immune system were demonstrated. However, the data available on this issue are limited, and the absence of an effect is largely inferred from the failure to observe an increase in infectious diseases among occupational and environmental cohorts exposed to PCBs.

Kidney Effects: To determine whether the literature supports an association between PCB exposure and kidney effects, 14 clinical studies and one mortality study were examined. Of the 14 clinical studies, nine involved occupational PCB exposure and five environmental PCB exposure. The evidence indicates no excesses in mortality or morbidity from diseases of the kidneys or urinary tract among human populations exposed to commercial PCB mixtures. While some measures of kidney function were occasionally reported as abnormal, there was no indication that the frequency of abnormalities was truly elevated above background. Furthermore, the frequency of abnormalities was not consistently related to PCB body burden, nor was there any indication that the sporadic functional abnormalities were related to clinically significant disease. Considering all of the evidence, there is no evidence for a causal association between PCB exposure and kidney dysfunction of any kind.

Gastrointestinal Effects: Five clinical studies of capacitor workers or transformer repairmen and four mortality studies of PCB-exposed workers were reviewed to determine whether there is an association between PCB exposure and gastrointestinal effects. The available evidence indicates no excess mortality or morbidity from diseases of the gastrointestinal tract in highly exposed workers. Studies of populations with lower exposures also failed to find an excess prevalence of any type of gastrointestinal disease. Although self-reported, non-specific, gastrointestinal symptoms were reported in some studies of PCB-exposed workers, no evidence indicates that the incidence of these symptoms was significantly higher than expected, or that the potential for confounding by concomitant exposure to solvents and other chemicals could be eliminated. In addition, physical examinations and clinical testing found no excesses of clinically-defined gastrointestinal diseases or dysfunction in the symptomatic workers. Overall,

there is no evidence to suggest that environmental exposure to PCBs adversely affects the gastrointestinal tract.

Musculoskeletal Effects: Nine clinical studies and one mortality study were evaluated to determine whether there is an association between PCB exposure and musculoskeletal effects. Of the nine clinical studies, four involved occupational exposure and five involved environmental exposure. While a few studies reported the frequencies of self-reported and non-specific musculoskeletal symptoms such as joint pain, interpretation of these data was hindered by the absence of appropriately matched controls, the failure to perform confirmatory physiological testing, and a lack of detail regarding the severity of pain, its constancy, and its relation to exposure duration or intensity. In no case were symptoms linked to clinical disease. Clinical chemistry analyses for uric acid and serum calcium failed to support an association between PCB exposure and musculoskeletal effects. Moreover, mortality due to bone diseases was not elevated in a large capacitor manufacturing cohort. Thus, the literature does not support a causal association between PCB exposure and musculoskeletal effects of any kind.

Nervous System Effects: To determine whether the literature supports an association between PCB exposure and nervous system effects, 16 clinical studies and four mortality studies were evaluated. Of the 16 clinical studies, seven involved occupational exposure and nine involved environmental exposure. A few studies reported an excess of subjective symptoms, but these symptoms were not specific to the nervous system. Physical examinations provided no evidence of clinical disease to explain the symptom occurrence, and all associations were confounded by exposures to other chemicals found in these work environments. Those studies examining the association between PCB exposure and diseases of the brain (such as Alzheimer's disease) were limited by small numbers of subjects, as well as failure to control for chemical confounders, particularly chemicals which are well-known neurotoxins. No significant elevations in mortality from neurological diseases were seen in the mortality studies. Therefore, there is insufficient evidence for a causal association between PCBs and neurological effects.

Genotoxic Effects: To determine whether the literature supported an association between PCB exposure and genotoxicity, three human *in vivo* studies, four *in vitro* studies using human cells, and numerous other *in vitro* and *in vivo* studies with either non-human species or non-mammalian test systems were evaluated. The studies provide no definitive evidence that occupational or environmental exposure to PCBs results in genotoxicity. All three studies of occupationally-exposed persons were confounded by non-PCB genotoxins and the *in vitro* studies using human cells are contradictory. As for the many other *in vitro* and *in vivo* studies, 82% were negative for genotoxicity. Therefore, when one considers all of the literature, there is little reason to believe that PCBs pose a significant genotoxic hazard to humans, especially at environmental exposure levels.

Reproductive Effects: To determine whether the literature supports an association between PCB exposure and reproductive toxicity, pertinent studies were divided into six

categories according to the reproductive endpoint examined. Eleven studies examined "physical parameters of offspring," eight studies examined "fertility endpoints," five studies examined "fetal loss," and two studies each examined "premature delivery," "hormonal effects," and "miscellaneous reproductive effects." Most of the studies involved environmental exposures to PCBs confounded by co-exposure to other organochlorine compounds. Collectively, the studies do not indicate that PCBs are male or female reproductive toxicants at environmental exposure levels.

One high-exposure study reported small statistical correlations between serum PCBs and gestational age and birth weight, but the authors concluded that the biological importance of the associations was likely negligible and, after considering several potentially-confounding covariables, the initial association between birth weight and PCB exposure became insignificant. Another high-exposure study reported lower than expected mortality rates for diseases of the genitourinary tract in both males and females. Although some low-exposure studies have reported various isolated correlations between PCB exposure and certain parameters of female reproductive function, these findings were undermined by measurement of clinically-insignificant changes, confounding by exposures to other chemicals, and by failure to control for other risk factors, to provide properly-matched controls, or to demonstrate a dose-response relationship. Additionally, several of the studies state that their associations could be due to chance alone and for no single reproductive endpoint is there a high degree of consistency in findings among studies. When the literature is considered as a whole, there is insufficient evidence for a causal association between PCB exposure and reproductive effects.

Mortality: Based on lethal PCB doses reported in animal studies, there is no reason for concern that acute PCB exposure would lead to lethality in humans. To determine whether the literature supports an association between PCB exposure and noncancer mortality, 15 human mortality studies were evaluated. There is no strong or consistent evidence to indicate that PCB exposures can increase noncancer causes of mortality. Moreover, the clinical studies have consistently demonstrated that PCBs are not acutely toxic, and that the only organ system that may be affected to a clinically significant degree is the skin. There is no evidence indicating a trend of increased noncancer diseases of any kind among PCB-exposed populations or that mortality was increased in a manner consistent with PCB exposure. Considering the above, as well as the absence of a mechanism for increasing overall mortality and the lack of elevated death rates among the most heavily PCB-exposed human populations, the existing literature does not support a causal association between PCB exposure and the risk of any kind of noncancer mortality.

The review reached the following overall conclusions:

- Some evidence indicates that skin and eye effects (e.g., eye irritation and burning, dermatitis), possibly including chloracne, are causally associated with high leveloccupational exposure to PCBs. It is clear that there is no causal

association between chloracne or other oculodermal effects and low-level environmental PCB exposure.

- The human data provide no support for a causal association between PCB exposure and any type of disease, dysfunction, or effect on the following organs or organ systems: liver, serum lipids or lipoproteins, cardiovascular/cerebrovascular system, lungs, blood, immune system, kidneys, gastrointestinal tract, musculoskeletal system, nervous system, and reproductive system. In addition, no causal associations were found for PCBs and genotoxicity or an increase in mortality.

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